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EXAMINER	
THOMAS, DAVID C	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,429	ROMMENS ET AL.	
	Examiner	Art Unit	
	DAVID C. THOMAS	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,21 and 23-53* is/are pending in the application.

4a) Of the above claim(s) *23-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,21 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/19/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed November 19, 2008 is acknowledged. Claim 1 (currently amended) and claims 2-11, 21 and 53 (original or previously presented) will be examined on the merits. Claims 23-52 were previously withdrawn. Claims 12-20 and 22 were previously canceled.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-11, 21 and 53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for diagnosing SDS based on some SBDS mutations associated with SDS, does not reasonably provide enablement for diagnosing SDS based on all SBDS mutations associated with SDS. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. As discussed below, there are only a limited set of SBDS mutations disclosed in the specification that are significant with respect to predicting whether a subject is suffering from SDS. These include the mutations 183_184TA>CT, 183_184TA>CT + 258+2T>C and 258+2T>C for which the claims are enabled.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-11, 21 and 53 are broadly drawn to methods for determining whether a subject is suffering from Shwachman-Diamond Syndrome (SDS) or is an SDS carrier based on the presence or absence of mutations in the Shwachman-Bodian-Diamond Syndrome (SBDS) gene. However, as will be further discussed, there is only a limited number of mutations disclosed in the specification and supported in the literature that provide enablement for the methods as claimed. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Working Examples

The specification has three working examples on pages 30-33. Example 1 is relevant to the elected claims, describing sequence analysis of the SBDS gene from several SDS-patients. Example 1 of the specification presents evidence that three SBDS mutations listed in Table 1 are significant with respect to predicting whether a

subject is suffering from SDS. These include 183_184TA>CT, 183_184TA>CT + 258+2T>C and 258+2T>C, which occurred in 50%, 5.1% and 4.4%, respectively, of patients in an initial study. These mutations have also been linked with SDS in more recent studies, as discussed below. Therefore, based on the disclosure in Example 1 of the specification as well as the supporting recent literature, the claims are enabled for only these three mutations.

Guidance in the Specification

The specification provides little evidence that the disclosed methods would lead to a successful method for determining whether a subject is suffering from Shwachman-Diamond Syndrome (SDS) or is an SDS carrier. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses that there is a reasonably strong correlation between three mutations found in the SBDS gene and the occurrence of the disease in patients. A number of other mutations are identified in Example 1 and Table 1 as being detected in samples from SDS patients. However, there is no support that these mutations would be useful in a panel of mutations for determining whether a subject is suffering from Shwachman-Diamond Syndrome (SDS) or is an SDS carrier. Furthermore, the specification has not provided definitive primers that can be used for amplification and detection of SBDS mutations since the primers described in the specification do not match those of the sequence listing, and therefore even the skilled artisan would be unable to use the methods of the invention.

The unpredictability of the art and the state of the prior art

There is a great unpredictability in the field of SDS research and the gene associated with this disorder, SBDS. Until 2003, there was no known gene associated with SDS. Prior to this, a number of studies suggested the disease was linked to various genetic loci on a number of different chromosomes. Finally, the genetic locus for SDS was narrowed to the centromeric region of chromosome 7 in 2001 (Goobie et al., Am. J. Hum. Genet. (2001) 68:1048-1054). Then in 2003 it was shown that mutations in the uncharacterized gene, SBDS, were linked to the disease (Boocock et al., Nature Genet. (2003) 33:97-101; the author list of this reference includes the current inventors), including a number of mutations included in Table 1 and claims 6 and 53 of the instant invention. As were presented in Example 1 and Table 1 of the disclosure, the only mutations that occur with high frequency among the total mutant SBDS alleles are 183_184TA>CT, 183_184TA>CT + 258+2T>C and 258+2T>C, which occurred in 26%, 2.5% and 46%, respectively, of total alleles (this data was presented as a percentage of mutant alleles rather than a percentage of patients). These three mutations were determined to arise through gene conversion due to recombination between SBDS and its pseudogene, and together account for 74% of the total mutant alleles (p. 99, column 1, lines 29-39). A number of other mutant alleles that are not gene conversion mutations occur at well less than 1% of the total mutant alleles. It is noted that about half of these non-gene conversion mutations listed in Table 1 and claims 6 and 53 were also reported by Boocock (see Boocock, Table 1), while Boocock reports an additional mutation, 635T>C, not present in the instant invention.

Since the landmark study of Boocock that definitively linked the SBDS gene to SDS, a number of more recent studies support the initial findings that the gene conversion mutations discovered by Boocock and shown in Table 1 of the specification are the most significant mutations relevant to determining whether a subject is suffering from Shwachman-Diamond Syndrome (SDS) or is an SDS carrier. In a recent review of SBDS gene mutations detected in SDS patients, most of the gene conversion mutations known to date include one or more of the same three mutations originally reported by Boocock, though sometimes in combination with additional mutations (Costa et al., Blood Cells, Molecules and Diseases (2008) 40:183-184, see Table 1). Several additional novel non-gene conversion mutations have been added to the list originally reported by Boocock.

An earlier studied noted the frequent occurrence of the known gene conversion mutations (such as 183_184TA>CT + 258+2T>C) as well as novel mutations associated with SDS (including 652C>T + 258+2T>C), but also reported several patients with SDS phenotypes but with no SBDS mutations detected (Woloszynek et al. Blood (2004) 104:3588-3590, see Table 1). Thus, while most SBDS mutations were harbored in patients with phenotypically-defined SDS, consistent with the study of Boocock that first linked such mutations with SDS in 2003, the fact that not all SDS patients have SBDS mutations suggests that SDS is a genetically heterogeneous disorder (Woloszynek et al. Blood (2004) 104:3588-3590). Thus, assays that rely on detecting only the known gene-conversion and non-gene conversion mutations may not diagnose all patients that are suffering from Shwachman-Diamond Syndrome (SDS) or are SDS carriers.

Furthermore, another study revealed that SBDS mutations may result in diseases phenotypically distinct from SDS. Samples from two patients revealed known mutations linked to SDS, yet the patients did not display the typical skeletal phenotype of SDS, but rather severe forms of neonatal spondylometaphysial dysplasia (SMD) (Nishimura et al. J. Med. Genet. (2007) 44:e73, pp. 1-5). One such patient had the recurrent gene conversion mutation 183TA>CT and a novel missense mutation, 79T>C, while a second patient has two recurrent gene conversion mutations, 183TA>CT and 258+2T>C (see Abstract). Several other SMD patients were found to have no SBDS mutations. Thus, while findings of the recurrent SBDS gene conversion mutations appear to be highly linked to SDS, clearly not all such mutations result in SDS, suggesting that SBDS mutations may give rise to variable phenotypes or that unknown mutations are also involved (Nishimura, p. 4, column 2, lines 5-20).

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is a significant number of parameters which would have to be studied to apply this method to determining whether a subject is suffering from SDS or is an SDS carrier, even based on the known mutations of the SBDS gene. Since studies suggest that SDS may be a genetically heterogeneous disorder, further experimentation would be required to search for other genes that may be associated with development of SDS. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where mutations in the SBDS often, but not always, indicate that a subject is suffering from SDS or is an SDS carrier, while some SBDS mutations may result in non-SDS disorders, the factor of unpredictability weighs heavily in favor of undue experimentation. Thus, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in determining whether a subject is suffering from SDS or is an SDS carrier, particularly in light of the limited set of SBDS mutations in Table 1 of the specification and claims 6 and 53 that are significantly associated with SDS. Furthermore, the specification has not provided definitive primers that can be used for amplification and detection of the SBDS mutations listed in Table 1 of the specification and claims 6 and 53. Thus, given the broad claims in an art whose nature is identified as unpredictable, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Allowable Subject Matter

4. Claims 1-11, 21 and 53 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to practice the invention commensurate in scope with the claims, as discussed above. However, the specification is enabling for diagnosing SDS based on some SBDS mutations. Furthermore, no prior art was found that teaches a method for determining whether a subject is suffering from SDS or is an SDS carrier based on the presence of these mutations in both or one SBDS alleles, respectively.

Response to Arguments

5. Applicant's arguments filed November 19, 2008 have been fully considered but they are not persuasive.

In response to the non-compliance letter of June 19, 2008, Applicant has corrected the defective sequence listing by way of an amendment filed September 19, 2008 and thus the requirement for compliance has been met. The Examiner acknowledges that the primers listed in the claims and specification used for amplification and detection of SBDS mutations are now properly identified.

The Examiner previously objected to several drawings that failed to show several features in color as described in the specification, and also to the lack of sequence identifiers in several drawings and figure legends. Applicant has filed an amendment on November 19, 2008 to correct these deficiencies and therefore the objections are withdrawn.

The Examiner previously objected to claim 1 for informalities, including spelling inconsistencies in the claim compared to the specification, as well as the lack of a definition of the acronym "SBDS". These have been corrected in the amendment of November 19, 2008 and the objection is withdrawn.

Claims 6 and 53 were previously rejected under 35 U.S.C. 112, second paragraph as being indefinite based on apparent discrepancies for numbering the mutations to match positions in the SBDS gene. Applicant has now explained the numbering system and cited a reference which also describes the numbering nomenclature used in the claims. The rejection is therefore withdrawn.

Finally, Applicant argues that the rejection of claims 1-11, 21 and 53 under 35 U.S.C. 112, first paragraph for alleged lack of enablement for diagnosing SDS based on all SBDS mutations should be withdrawn. In particular, Applicant argues that the present claims are not directed to diagnosing SDS based on all SBDS mutations, but only SBDS mutations associated with SDS. As previously indicated by the Examiner, only three mutations listed in Table 1 of SDS-associated mutations are enabled since only these mutations are disclosed in the specification to have significance with respect to predicting whether a subject is suffering from SDS. The Examiner asserts that since other mutations besides 183_184TA>CT, 183_184TA>CT + 258+2T>C and 258+2T>C may be associated with SDS, but yet only these three mutations are definitive for diagnosis of SDS, the claims as written are not enabled for diagnosis based on all SBDS mutations associated with SDS. Furthermore, since not all SDS patients have SBDS mutations (Woloszynek et al. Blood (2004) 104:3588-3590, see Table 1) and

since some patients have the classic gene conversion mutations without the typical skeletal phenotype of SDS (Nishimura et al. J. Med. Genet. (2007) 44:e73, pp. 1-5, see Abstract), the current invention is better described as a method for increasing the likelihood for determining whether a subject is suffering from SDS or is an SDS carrier based on detection of one or more of the three mutations cited above. Therefore, the rejection of claims 1-11, 21 and 53 under 35 U.S.C. 112, first paragraph is maintained.

Summary

6. Claims 1-11, 21 and 53 are rejected. No claims are allowable.

Conclusion

7. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320 and whose fax number is 571-273-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David C Thomas/
Examiner, Art Unit 1637

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637